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13. ABSTRACT (Maximum 200 Words)

We are continually conducting clinical experiments at the UConn Health Center and Hartford Hospital. The statistical analysis of the first 65 cases (including 8 cases of cancers and 57 cases of benign lesions) shows strong correlation between the total hemoglobin concentration and malignance. There is about two-fold increase in the total hemoglobin concentration for cancers compared with the typical values for benign lesions. This agrees with our hypothesis that optically available parameters can significantly improve the accuracy of breast cancer detection.

To further improve the performance of optical imaging system, we are pursuing the time-resolved method. We have developed a time-resolved diffusive optical tomography system via a novel spread spectrum approach. A low power (~5 mW) laser diode modulated with pseudo-random bit sequences replaces the short pulse laser used in conventional time-resolved optical systems, while the time-resolved transmittance is retrieved by correlating the detected signal with the stimulation sequence. Temporal point spread functions of diffusive light propagating through a turbid medium have been measured with remarkably low noise levels. 2-dimensional scanning imaging experiments were performed to demonstrate the great potential of this new imaging technique. Sub-nanosecond temporal resolution (~0.9 ns) has been achieved.

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Table of Contents

Cover.....1

SF 298.....2

Table of Contents.....3

Introduction.....4

Body.....4

Key Research Accomplishments.....7

Reportable Outcomes.....7

Conclusions.....8

References.....8

Appendices.....

Annual Report

PI: Nan Guang Chen

INTRODUCTION:

The diagnosis of solid benign and malignant tumors presents a unique challenge to all noninvasive imaging modalities. Ultrasound has been used to differentiate simple cysts from solid lesions. However, the overlapping appearances of benign and malignant lesions make ultrasound less useful in differentiating solid lesions, resulting in a large number of benign biopsies. Optical mammography using near-infrared diffusive light has the great potential to provide the functional imaging parameters in terms of tumor hemoglobin concentration, blood oxygen saturation, and other tumor distinct characteristics. These parameters can help differentiate benign from malignant lesions. However, optical mammography, when used alone, suffers from low spatial resolution and target localization uncertainty due to intensive light scattering. Our aim is to combine diffused light imaging with ultrasound in a novel way for the detection and diagnosis of solid lesions. Initial findings of two early stage invasive carcinomas, one combined fibroadenoma and fibrocystic change with scattered foci of lobular neoplasia/lobular carcinoma in situ, and 16 benign lesions are reported in this paper. The invasive cancer cases reveal about a two-fold increase in the total hemoglobin concentration (mean 119 mmol) than benign cases (mean 67 mmol), which suggests that the discrimination of benign and malignant breast lesions might be enhanced by optically available parameters.

Beside the clinical studies with ultrasound assisted optical imaging system. We are developing time-resolved method to improve the performance of optical imagers. Time-resolved method is well known for its potential to help diffusive optical tomography achieve higher spatial resolution. The temporal point spread function (TPSF) of diffusive light contains the complete set of information that can be used for image reconstruction. Considering typical values of the mean optical pathlength, the temporal resolution of a time-resolved diffusive optical tomography system should be less than a few nanoseconds. Conventional time-resolved optical systems are based on pulse light sources such as flash lamps and lasers. While short enough light pulses can be generated by picosecond or even femtosecond lasers, the speed of optodetectors and following electronics generally limit the overall temporal resolution of the entire system. The time correlated single photon counting (TCSPC) method is popular because it can achieve sub-nanosecond temporal resolution with reasonably good signal to noise ratio and dynamic range. However, its data acquisition time is usually very long. In this report, we present an experimental implementation of a novel time-resolved DOT system. It has significant advantages over existing technologies, including high data acquisition speed, superior signal to noise ratio, and low costs.

BODY:

We have investigated the optical tomography using a priori lesion structural information provided by co-registered US. The light guides using optical fibers are coupled to a hand-held probe with a commercial ultrasound transducer deployed in the middle. Preliminary results of 19 solid lesions have shown that two early stage invasive cancers have shown

two-fold high total hemoglobin concentration than a group of benign lesions. Preliminary results of 4 advanced cancers have shown heterogeneous total hemoglobin distributions and the distributions correlate with histological micro-vessel density counts. In this paper, we further demonstrate the clinical potential of optical tomography assisted with US localization in distinguishing benign from malignant lesions, and we compare optical tomography with Doppler US on mapping tumor angiogenesis.

Clinical studies were performed at the Radiology Departments of Hartford Hospital and UConn Health Center. The IRB committees of both institutions approved the human subject protocol. Patients who were scheduled for ultrasound guided biopsy were recruited to the study. Ultrasound images and optical measurements were acquired simultaneously before biopsy procedures at multiple locations including the lesion region, a normal region of the same breast, and a normal symmetric region of the contralateral breast. The optical data acquired at normal regions were used as reference for calculating the scattered field caused by lesions. For Doppler US measurements, any persistent color Doppler signals were taken to represent blood vessels. The location of the vessels with respect to the lesion was documented as peripheral to the lesion, within the lesion, or both. The details of our dual-mesh optical imaging reconstruction algorithm have been described in Ref. Briefly, the NIR reconstruction takes advantages of ultrasound localization of lesions and segments the imaging volume into finer grid in lesion region and coarser grid in non-lesion regions. A modified Born approximation is used to relate the scattered field measured at the source-detector pairs to absorption variations in each volume element of two regions within the sample. With this dual-mesh scheme, the inverse optical reconstruction is well-conditioned and converges in few iterations.

Table 1 lists all the measured parameters of the 19 cases [from left to right: biopsy result, lesion size measured by ultrasound in x and z dimensions (becauselesions are small, the lesion size in y is similar to that measured in the x dimension), region of interest (ROI) used for fine-mesh NIR imaging, FWHM measured from NIR imaging, maximum absorption coefficients measured at both wavelengths, maximum and average total hemoglobin concentrations (the average is computed within FWHM)]. For the two invasive cancer cases, NIR parameters are given for two different ROIs and the results show that the choice of ROI has negligible effects on the absorption and hemoglobin measurements. The benign group of fibroadenoma (15 cases) and hyperplasia (1 case) has an average of 67 mmol (...17.0 mmol), the combined fibroadenoma and fibrocystic change with noninvasive neoplasia/carcinoma *in situ* case has a maximum of 48 mmol, and the invasive cancer group of two cases has shown about two-fold greater average of 119 mmol (...1.6 mmol). If average total hemoglobin concentration is used, the values are 46 (...11.3), 30, and 86 (...2.12) mmol for the three corresponding groups, respectively.The malignant group also presents about two-fold greater average hemoglobin concentration than that of the benign group. The average sizes of lesions of the three groups measured by ultrasound are 1.05 (...0.3), 1.1, and 0.9 (...0.07) cm, respectively. The lesion size is the geometric mean of diameters measured in x and z dimensions. Fig. 1 shows the statistic analysis of more cases acquired recently (total 65 cases).

Table 1. Measured parameters of 19 cases

Reference Number	Biopsy Results	Lesion Size (Ultrasound) [cm]	ROI	FWHM (NIR) [cm]	Max μ_a [cm^{-1}], 780 nm	Max μ_a [cm^{-1}], 830 nm	Max Total Hb [μM]	Average Total Hb [μM]
13	Invasive cancer	0.9 × 0.6	6 × 6 × 1	3.5	0.28	0.24	123	87
			10 × 10 × 1	3.5	0.27	0.24	122	88
25	Invasive cancer	0.8 × 0.5	6 × 6 × 1	2.0	0.22	0.26	115	84
			10 × 10 × 1	2.1	0.22	0.26	115	84
32	Fibrocystic and lobular neoplasia/carcinoma	1.1 × 1.1	10 × 10 × 1.2	6.1	0.12	0.08	48	30
11	Fibroadenoma	1.2 × 0.8	8 × 8 × 1	4.9	0.11	0.10	49	37
8	Fibroadenoma	2.2 × 1.3	8 × 8 × 1.6	2.7	0.07	0.03	24	16
9	Fibroadenoma	0.9 × 0.7	8 × 8 × 1	4.9	0.15	0.18	77	52
7	Fibroadenoma and sclerosing adenosis with extensive calcification	1.0 × 0.6	10 × 10 × 1	3.8	0.16	0.11	59	41
17	Fibrocystic changes	0.6 × 0.7	10 × 10 × 1	5.8	0.16	0.16	76	53
20	Fibroadenoma	1.2 × 0.6	10 × 10 × 1	5.7	0.14	0.14	67	45
30	1: Fibrocystic change	1.7 × 1.1	8 × 8 × 1.3	4.0	0.10	0.15	59	39
30	2: Sclerosing adenosis and epithelial hyperplasia without atypical	1.4 × 1.2	8 × 8 × 1.3	4.0	0.15	0.23	88	57
22	Fibroadenoma	1.0*	10 × 10 × 1.5	3.7	0.15	0.15	72	46
36	Fibroadenoma	1.9 × 0.9	9 × 9 × 1	4.7	0.13	0.18	73	50
28	Fibroadenoma	1.9 × 1.1	9 × 9 × 1.3	4.2	0.14	0.16	71	45
33	Fibroadenoma	1.2 × 0.7	10 × 10 × 1	7.0	0.13	0.13	61	44
37	Fibroadenoma	0.8 × 0.6	8 × 8 × 1	6.0	0.16	0.18	80	53
35	Fibroadenoma	1.3 × 1.3	9 × 9 × 2	4.3	0.14	0.15	59	41
38	Hyalinized fibroadenoma	0.8 × 0.4	6 × 6 × 1	2.5	0.17	0.22	90	67
29	Atypical ductal hyperplasia	1.1 × 0.8	9 × 9 × 1	3.7	0.10	0.17	64	44

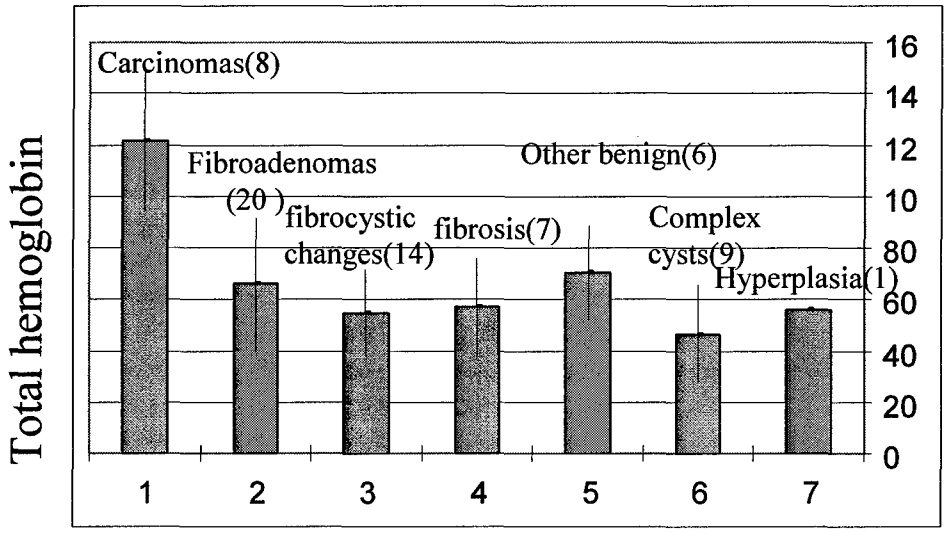

Fig. 1. Statistic analysis of 65 cases.

In addition to our clinical studies, we have been investigating the time-resolved method aiming at high quality optical mammography via a novel approach. Fig. 2. shows a prototype system we developed recently. Pseudo-random bit sequences (PRBS) are generated continuously at a 622 Mb/s rate by a network analyzer transmitter A 5 mW laser diode at 808 nm is used as the light source, which is amplitude modulated with the PRBS. The transmitted and/or reflected light is detected by a Silicon Avalanche Photodiode (APD). The opto-electrical signal is pre-amplified by a low noise

transimpedance amplifier, and then fed to the RF port of a frequency mixer. The local oscillation (LO) port of the mixer is connected to the reference signal, which is identical to the laser diode modulation sequence except time shifted by a variable delay line. Coaxial cables of different lengths are switched to adjust the delay time. A personal computer acquires the waveforms from the detection channel with a data acquisition board and the waveform amplitudes are translated to time-resolved intensities. The temporal resolution achieved is 0.9 ns. We've acquired 2-D shadowgraphs with various time delays for different targets embedded in thick tissue phantoms. The results agrees with the theoretical prediction that early arriving photons can lead to higher spatial resolution.

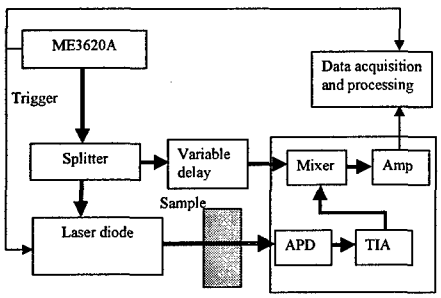

Fig. 2. Prototype 1-channel time-resolved diffuse optical tomography system based on pseudo-random bit sequences.

KEY RESEARCH ACCOMPLISHMENTS:

- Analyzed 65 cases including 8 cases of cancers and 57 cases of benign lesions.
- Built a prototype spread spectrum time-resolved diffuse optical imaging system.
- Performed preliminary experimental study with the prototype time-resolved system.

REPORTABLE OUTCOMES:

Journal papers:

[1] N. G. Chen, M. Huang, H. Xia, D. Piao, E. Cronin, and Q. Zhu, "Portable near infrared diffusive light imager for breast cancer detection," *Journal of Biomedical Optics*, Vol. 9, No. 3, pp. 504-510 (2004).

[2] B. H. Yuan, N. G. Chen, and Q. Zhu, "Absorption and Emission Properties of Indocyanine Green in Intralipid Solution," *Journal of Biomedical Optics*, Vol. 9, No. 3, pp. 497-503 (2004).

[3] N. G. Chen and Q. Zhu, "Time-resolved diffusive optical tomography using pseudo-random sequences," *Optics Express*, Vol. 11, No. 25, pp 3445-3454 (2003).

[4] Q. Zhu, M. Huang, N. G. Chen, K. Zarfos, B. Jagjivan, M. Kane, S. H. Kurtzman, "Ultrasound-guided optical tomographic imaging of malignant and benign breast lesions: initial clinical results of 19 cases," *Neoplasia*, Vol. 5, No. 5, pp 379-389 (2003).

[5] M. Huang, T. Xie, N. G. Chen, and Q. Zhu, "NIR imaging reconstruction with ultrasound localization," *Applied Optics*, Vol 42, No. 19, pp 4102-4114 (2003).

Presentations:

N. G. Chen, Quing Zhu, "Prototype time-resolved diffusive optical imaging system," OSA biomedical optics topical meetings, Miami beach, 2004.

FUNDING APPLIED FOR:

[1] Nan Guang Chen (PI), "Diffuse optical tomography based on molecular transient absorption: a new approach toward breast cancer early detection," submitted to DoD breast cancer research program (Concept Award, rejected).

[2] Nan Guang Chen (PI), "Time-resolved diffuse optical imager for breast cancer early detection," submitted to DoD breast cancer research program (Idea Award, pending).

CONCLUSIONS:

I have successfully finished Task 2 specified in the statement of work of my proposal. Preliminary results obtained from 8 invasive early stage cancers and 57 benign lesions have shown that malignant cancers of 1 cm in size present an average of about 120 μ mol/liter maximum total hemoglobin concentration while the benign group has an average of 67 μ mol/liter. A nearly two hold higher contrast has been obtained. A prototype spread spectrum time-resolved system has been developed. Experimental results obtained with this prototype system have demonstrated the feasibility and great potential of this new method.

References:

[1] N. G. Chen, M. Huang, H. Xia, D. Piao, E. Cronin, and Q. Zhu, "Portable near infrared diffusive light imager for breast cancer detection," *Journal of Biomedical Optics*, Vol. 9, No. 3, pp. 504-510 (2004).

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